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Polymorphism of (Z)-3-Bromopropenoic acid: a high and low Z' pair

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ABSTRACT

Two polymorphic forms of (Z)-3-Bromopropenoic acid are reported. Form I (monoclinic, $P2_1/c$) with $Z' = 1$ is obtained from a range of solvents while Form II (monoclinic, $P2_1/n$) with $Z' = 4$ can be prepared only from either benzene or toluene. Both forms are isolated at room temperature. The molecules in both polymorphs interact with one another through similar dominant hydrogen bonding motifs; however, the packing arrangement differs in the prevalence of weaker hydrogen bonds in the metastable Form II. Analysis of this high and low Z' polymorphic pair using differential scanning calorimetry, grinding and slurry experiments, coupled with lattice energy calculations suggests that the low Z' form I is the most stable under ambient conditions. 2D fingerprint plots derived from Hirshfeld surfaces highlight the more extensive hydrogen bonding in Form II while Form I is more densely packed. This polymorphic pair may be a candidate for the role of solution pre-aggregation in the formation of high Z' forms.

Introduction

Crystal polymorphism,¹ the phenomenon of different crystal forms of the same molecule that have different arrangements and/or conformations in the solid state, has been known for more than 180 years since the 1832 report of the polymorphism of benzamide.² Different crystal forms display different physico-chemical properties such as melting point, dissolution rate, solubility and bioavailability.³⁻⁵ Compounds that crystallize with $Z' > 1$, i.e., more than one molecule in the asymmetric unit, are of considerable interest because there is some debate concerning the (likely multiple) explanations of the occurrence of structures with $Z' > 1$. It has been suggested that the phenomenon may arise from crystal nucleation and growth factors, and/or that crystals may pack with a high Z' asymmetric unit for structural reasons arising from limitations on the optimal packing of the molecular shape and simultaneous accommodation of optimal intermolecular interactions.⁶ A variety of explanations have been put forward to rationalize structures with high Z' values and current opinion has been summarised in a recent review.⁷ It may well be the case that because the Z' parameter is a simple one encompassing complex solid state behaviour, there may well be a number of different underlying causes depending on the system studied. In some cases it has been shown that structures with $Z' > 1$ are less stable than their $Z' = 1$ counterparts,⁸ while in other cases structures with $Z' > 1$ have no known $Z' = 1$ polymorph or a higher Z' structure is in fact the most stable.⁷ Elucidating the relative stability of polymorphic systems involving both $Z' > 1$ and $Z' = 1$ forms can make a considerable impact on this debate as the body of evidence grows. In this work, we report preparation and analysis of two polymorphs of (Z)-3-Bromopropenoic acid, a simple halogen-containing unsaturated carboxylic acid. (Z)-3-Halopropenoic acids are of interest because they have been reported to have specific cotton defoliating activity and crop desiccant properties.⁹

Results and Discussion

Crystal and Molecular Structure Description of Forms I and II

The crystallization of (Z)-3-Bromopropenoic acid (**BPA**) was attempted using a variety of different crystallization methods including slow evaporation of various solvents; melt and sublimation techniques. **BPA** has three hydrogen bond donors and two oxygen atom acceptors. The screening resulted in the isolation of two different polymorphic modifications dubbed forms I and II. Form I was obtained by slow evaporation of saturated solution of ethanol under ambient conditions. The single crystal X-ray structure analysis revealed that the Form I crystallizes in space group $P2_1/c$ with $Z' = 1$. Crystallographic parameters are given in Table 1. Arrangement of the molecules in three-dimensions in the crystal lattice is shown in Figure 1(b). Figure 1(a) illustrates the hydrogen bonding interactions in the crystal structure of Form I. The molecules are linked through $O1-H1\cdots O2$ ($O1\cdots O2$ 2.683(3) Å, $O1-H1\cdots O2$ 178°) hydrogen bonded carboxylate dimeric units forming an $R_2^2(8)$ motif.¹⁰ The dimeric units interact through the bromo and carboxylic acid oxygen atoms forming $Br1\cdots O1$ halogen bonds of 3.18 Å.¹¹

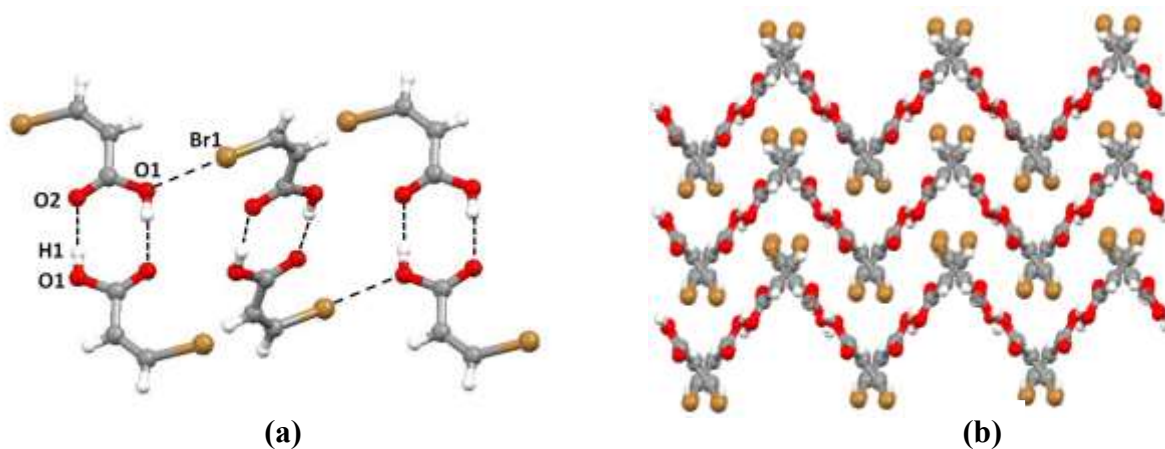


Figure 1. X-ray crystal structure of form I (a) Hydrogen and halogen bonding interactions (b) crystal packing arrangement.

Single crystals of Form II were obtained by crystallization of **BPA** from benzene or toluene. The material adopts the monoclinic space group $P2_1/n$ with $Z' = 4$, in contrast to Form I which has only a single molecule in the asymmetric unit. Form II consists of 2D layers of hydrogen and halogen bonded molecules (Figure 2(b)). Each of these layers consists of O-H \cdots O hydrogen bonded $R_2^2(8)$ network formed between two symmetrically inequivalent molecules (shown in different colours) as shown in Figure 2a. The halogen bonding network is incomplete with two of the four unique bromo substituents not interacting with oxygen acceptors and instead an unusual $R_2^2(7)$ hydrogen bonded pattern is formed via a CH \cdots O and a long CH \cdots Br interaction. The remaining two bromo substituents interact with both double bonded and single bonded oxygen atoms of the carboxylic acid groups forming Br \cdots O halogen bonds (3.24–3.34 Å). This contrasts to Form I in which halogen bonding is observed for every molecule between the bromo substituents and the single bonded OH group of the carboxylic acid. In addition, there is further C-H \cdots O hydrogen bonding is observed between trimeric units which is absent in Form I. The characteristics of hydrogen bonds are given in Table 2.

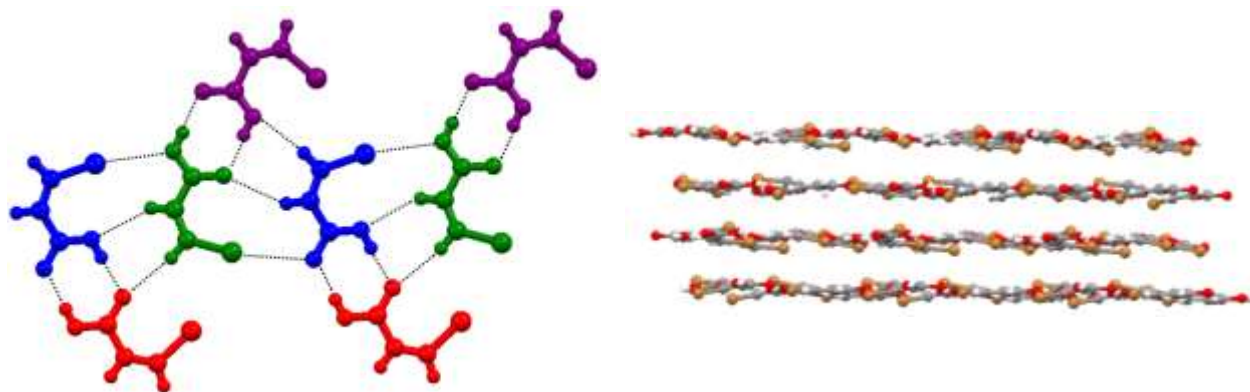


Figure 2. (a) Hydrogen bonding between the molecules observed in Form II of **BPA**, and (b) arrangement of molecules in three dimensions.

Table 1. Crystallographic data for Forms I and II of **BPA**.

	Form I	Form II
empirical formula		C ₃ H ₃ O ₂ Br
formula weight		150.96
crystal habit	Plates	Plates
crystal system	Monoclinic	Monoclinic
space group	<i>P</i> 2 ₁ / <i>c</i>	<i>P</i> 2 ₁ / <i>n</i>
<i>a</i> (Å)	5.4681(5)	10.7945(4)
<i>b</i> (Å)	8.3737(8)	13.4995(5)
<i>c</i> (Å)	10.0486(9)	13.1036(4)
α (deg)	90	90
β (deg)	103.037(5)	102.981(2)
γ (deg)	90	90
<i>V</i> (Å ³)	448.25(7)	1860.66(11)
<i>Z</i>	4	16
<i>D</i> _{calc} (g cm ⁻³)	2.237	2.155
<i>T</i> (K)	120	120
μ (mm ⁻¹)	9.014	8.686
2 θ range (deg)	3.2-30.1	2.2-27.9
<i>F</i> (000)	288	1152
No. parameters	55	217
GOF on <i>F</i> ²	1.0270	1.0174
<i>R</i> ₁ [<i>I</i> > 2 σ (<i>I</i>)]	0.0270	0.0353
w <i>R</i> ₂	0.0666	0.0618
$\Delta\rho_{\min}/\Delta\rho_{\max}$ (e Å ⁻³)	-0.98, 1.20	-1.39, 1.39

Table 2. Hydrogen Bond Parameters (distances, Å and angles, deg)

	Form I		Form II	
	D···A	\angle D-H···A	D···A	\angle D-H···A
O-H···O	2.683(6)	179.9	2.612(2)	179.9
			2.634(7)	179.9
			2.643(5)	179.9
			2.653(4)	179.9
C-H···O			3.430(6)	164.5
			3.435(3)	146.2
			3.528(8)	170.2
			3.603(4)	149.5

Stability relationship between Forms I and II

Differential scanning calorimetry (DSC) thermograms of Forms I and II were recorded using a heating rate of $2\text{ }^{\circ}\text{C min}^{-1}$, and it was found that both forms show a single sharp melting endotherm as shown in Figure 3. While Form I showed a melt with a peak at $60.1\text{ }^{\circ}\text{C}$ and onset of $59.6\text{ }^{\circ}\text{C}$ the corresponding endotherm for Form II was observed at 58.1°C , onset $57\text{ }^{\circ}\text{C}$. No phase transition is observed on heating either form. Form I melts at a slightly higher temperature than Form II suggesting that form I is the most stable close to the melting point. The stability relationship between the forms was further probed by grinding and slurry experiments.

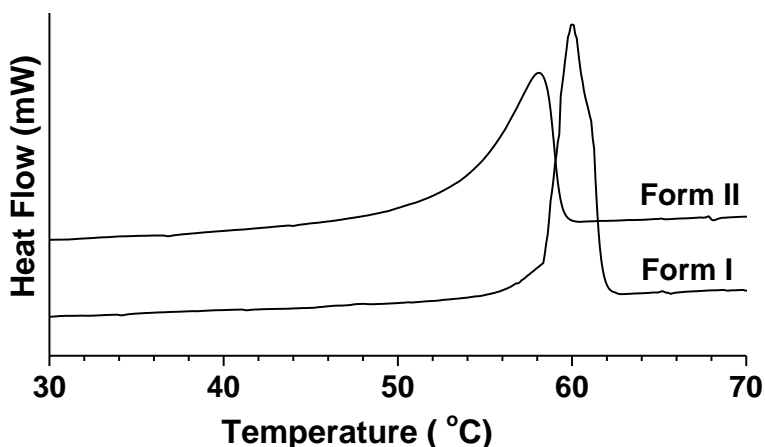


Figure 3. DSC heating traces of Forms I and II.

The effect of solid-state grinding/milling during formulation and drug development has been reported to have an effect on polymorphic form.¹² It is therefore important to establish the stability relationship between polymorphic forms as metastable forms may transform to more stable form upon grinding/milling. In the present case of **BPA**, both neat grinding (NG) and liquid-assisted grinding (LAG) experiments¹³ were carried out on both Forms I and II. LAG experiments were performed by adding few microlitres of various solvents (methanol, ethanol, chloroform, acetone, propanol, isopropanol, acetonitrile, benzene and water) followed by grinding in a ball

mill (see experimental section). Analysis of the PXRD patterns for the resulting products showed that Form II converted to Form I, however, Form I remains same under identical experimental conditions (Figure 4). These experiments suggests that Form I is more stable under ambient conditions and can be prepared easily from Form II by any form of grinding.

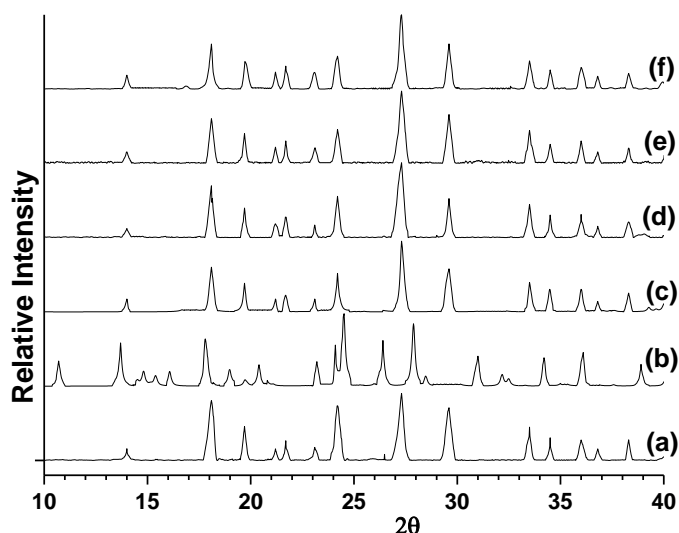


Figure 4: PXRD patterns of (a) Form I, (b) Form II, (c) NG of Form I, (d) LAG of Form I (e) NG of Form II, and (f) LAG of Form II.

The phase transformation (Form II to I conversion observed in both NG and LAG experiments) was also verified by slurry experiments performed in methanol and water medium and also 1:1 mixture of Forms I and II at room temperature. Form I and II were slurried for 24h and resulting solids were filtered and dried. PXRD analysis of the samples revealed that Form I remained unchanged, however, Form II converted to Form I (Figure 5). The observations made in the grinding and slurry experiments indicate that Form I is the more stable form across the entire temperature range from room temperature up until melting and hence the two forms are monotropically related. Such a transformation from Form II to I occurs due to the dissolution of Form II followed by recrystallization of Form I.

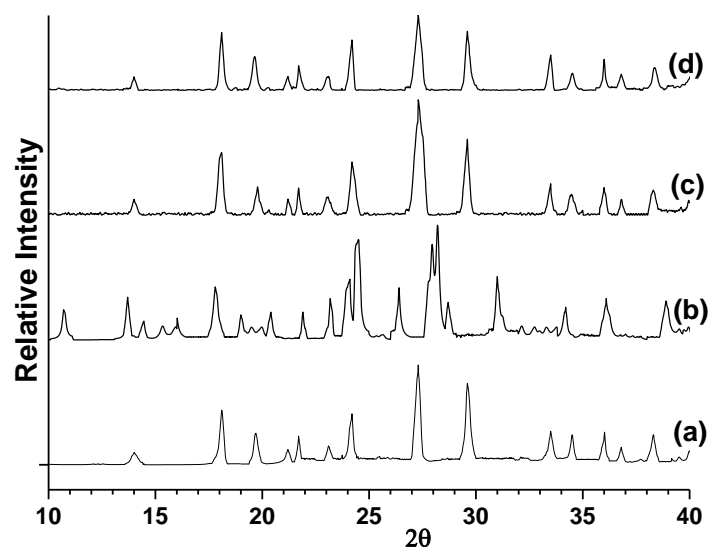


Figure 5. PXRD patterns of (a) Form I, (b) Form II and slurry experiments on (c) Form I (d) Form II.

Hirshfeld surface analysis of the two structures using the program Crystal Explorer¹⁴ clearly highlights the major differences in the interactions in the two forms. The carboxylic acid dimer hydrogen bond is common to both forms and is evident as two large spikes at the bottom right of each plot. However this interaction is not likely to be structure directing. The evident difference in the two polymorphs is the much greater prevalence of CH \cdots O interactions in form II (seen as additional spurs either side of the main OH \cdots O interactions, which are far less evident in form I (Figure 6). In Form I, each molecule participates in two hydrogen bonds while in Form II each symmetry independent molecule participates in six hydrogen bonds given the added CH \cdots O interactions. Hence this polymorphic pair exhibits a higher density, better packed thermodynamically stable Form I and a lower density Form II with more directional interactions. The dominant effect of weaker interactions in determining polymorphic form has been noted previously.¹⁵ The role of increased CH \cdots O interactions in stabilizing high $Z' > 1$ polymorphs has also been commented on.¹⁶

(a)

(b)

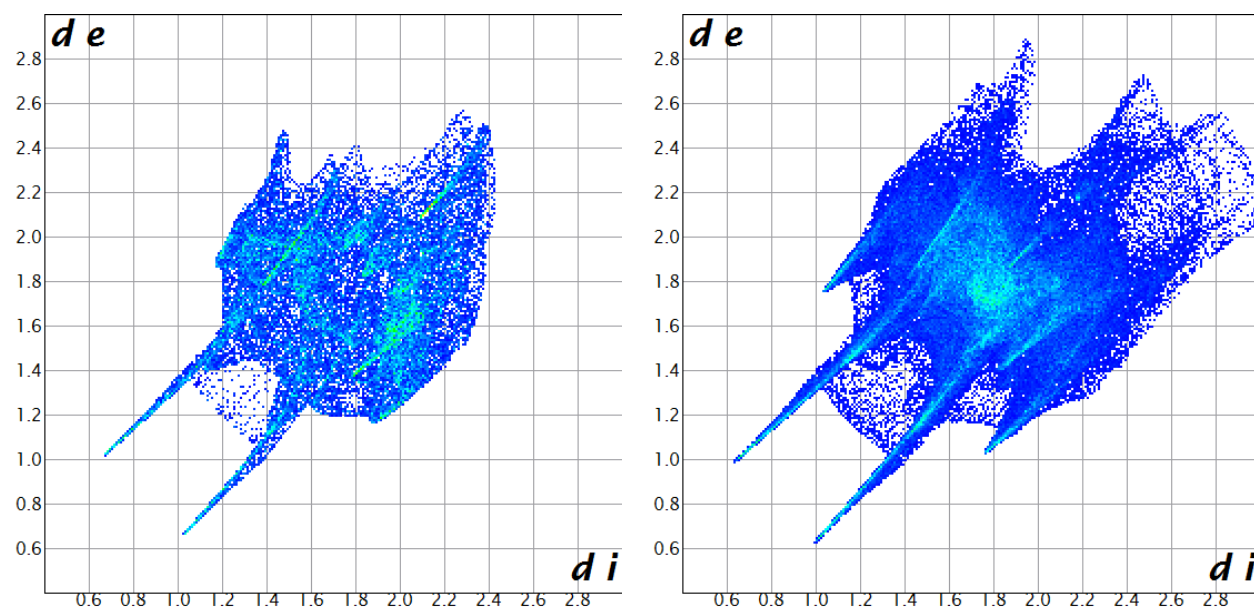


Figure 6. Hirshfeld 2D fingerprint plots of (a) Form I and (b) Form II.

The greater stability of form I is supported by UNI intermolecular potentials¹⁷ implemented in the CSD Mercury package which give a total packing energy of $-88.4 \text{ kJ mol}^{-1}$ for Form I and $-78.8 \text{ kJ mol}^{-1}$ for Form II. In form I the dominant intermolecular interaction potential is that of the carboxylic acid dimer ($-47.2 \text{ kJ mol}^{-1}$). One of the two independent carboxylic acid dimers is weaker in Form II (-47.2 and $-45.8 \text{ kJ mol}^{-1}$). Interactions above and below the intermolecular plane are also weaker in form II. Hence it seems that Form II is an entirely metastable, kinetic form and could be an example of a system in which clustering in solution prior to crystallization is responsible for the high Z' observed in the crystal structure, particularly since this form is obtained from non-polar solvents in which directional intermolecular interactions such as hydrogen and halogen bonding are expected to be important.

Conclusion

In conclusion, preparation and analysis of two polymorphs of (Z)-3-Bromopropenoic acid (**BPA**) have been reported and the different forms characterized with $Z' = 1$ and 4, respectively. Crystal structure analysis reveals that both the forms are clearly distinguishable in terms of the arrangement of molecules in the crystal lattice. In both the forms, molecules interact through O-H \cdots O hydrogen bonded carboxylic acid dimer and Br \cdots O halogen bonding. In Form II, however, molecules also interact through C-H \cdots O hydrogen bonding with all the atoms involved in hydrogen bonding, while the halogen bonding is incomplete. Forms I and II are monotropically related with form I the most thermodynamically stable form across the entire temperature range studied. The metastable Form II is obtained from non-polar solvents and may be an example of a system in which clustering in solution prior to crystallization is responsible for the high Z' observed in the crystal structure. This interpretation is perhaps supported by the lack of a direct solid-solid phase transition from form II to form I upon heating in the DSC.

Experimental Section

Synthesis of (Z)-3-Bromopropenoic acid

Synthesis of (Z)-3-bromopropenoic acid was carried out as reported in the literature.¹⁸

Chemicals and Crystal Growth: Propiolic acid was purchased from Sigma-Aldrich. HPLC grade solvents were used for crystallization. Crystallization was carried out from a variety of commonly available solvents such as methanol, ethanol, propanol, isopropanol, acetonitrile, acetone, acetyl acetone, diethyl ether, chloroform, carbon tetrachloride, benzene, and toluene from which Forms I and II were isolated. Crystals of Form I (space group $P2_1/c$, $Z' = 1$), as

plates, were obtained in many cases with measured crystal being obtained by crystallization from ethanol. Form II (space group $P2_1/n$, $Z' = 4$), also as plates, was obtained by crystallization from either benzene or toluene.

Grinding Experiments. Grinding was performed using a Retsch Mixer model MM200 with 10 mL stainless steel grinding jars and two stainless steel grinding balls of 7 mm diameter. In a typical experiment, 200 mg was used for grinding. Liquid assisted grinding experiments were carried out by adding 30 μ L of a solvent prior to the grinding. The samples were then ground in the ball mill for 30 min at 30Hz.

Single-crystal X-ray Diffraction. Details of the single crystal X-ray diffraction intensity measurements and refinements are given in Table 1. All operations were performed on a Bruker-Nonius Kappa Apex2 diffractometer, using graphite-monochromated $\text{MoK}\alpha$ radiation ($\lambda=0.7107$ Å). All diffractometer manipulations, including data collection, integration, scaling, and absorption corrections for these forms were carried out using the Bruker Apex2 software.¹⁹ Preliminary cell constants were obtained from three sets of 12 frames. Data collection for Forms I and II was carried out at 120K, using a frame time of 20 sec and a detector distance of 60 mm. The optimized strategy used for data collection consisted of four phi and six omega scan sets, with 0.5° steps in phi or omega. From the systematic absences, the observed metric constants and intensity statistics, space groups $P2_1/c$ and $P2_1/n$ were chosen for Forms I & II respectively at the beginning; subsequent solution and refinement confirmed the correctness of the choice. The structures were solved using SIR92 and subsequent electron-density difference syntheses²⁰ and refined (full-matrix-least squares) using the Oxford University Crystals for Windows program.^{21,22} All non-hydrogen atoms were refined using anisotropic displacement parameters,

while H atoms were refined using isotropic displacement parameters. Crystallographic data (excluding structural factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre and allocated the deposition numbers CCDC 1035863-1035864. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EW, U.K. (E-mail:deposit@ccdc.cam.ac.uk).

PXRD: Powder X-ray diffraction measurements were carried out with a Rigaku Dmax 2500 diffractometer using Cu K α radiation ($\lambda = 1.5418 \text{ \AA}$). The sample holder was a copper block, and a very thin layer of powder sample was pressed on this block. The patterns were collected in the 2θ range of 5-50° with a step size of 0.02° and 1.0s counting per step. The PXRD patterns were plotted using OriginPro 7.5.

Thermal Analysis. The DSC experiments were performed using a DSC 1 Star System with STARe Excellence Software from Mettler-Toledo AG. Samples (~3-4 mg) were placed in Al crucibles after surface-drying on filter paper. The sample was heated from 28 °C to 80 °C at a rate of 5 °C/min and purged with a stream of flowing nitrogen.

ASSOCIATED CONTENT

Supporting Information. Crystallographic information files (CIF)

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